

REMARKS

With this amendment, Claims 1 and 2 are pending. Claims 3 and 31 have been cancelled.

Claim 1 has been amended to recite a method of testing for “atopic dermatitis” and the expression level of a gene or genes encoding the TR3, TINUR or TR3 and TINUR receptor protein in “eosinophil cells”. Support for these amendments can be found throughout the Specification and, in particular, at page 4, lines 12-14 and 24-27; page 11, lines 29-33 and page 17, lines 7-13.

No new matter has been added. Further remarks are set forth below.

Rejection of Claims 1-3 and 31 Under 35 U.S.C. § 112, First Paragraph- Enablement

Claims 1-3 and 31 are rejected under 35 U.S.C. § 112, first paragraph for scope of enablement. The Examiner states that “[a]pplicant is enabled for diagnosing atopic dermatitis by the recited methods, but not for all allergic diseases. Applicants have not shown how to make and use the invention for all allergic diseases.” (Office Action at page 2, paragraph 4 (4.)).

Applicants respectfully disagree for the reasons of record (see Amendment filed February 3, 2006 at pages 4-11). However, in order to expedite prosecution of this application, Claim 1 has been amended to recite a method of testing for “atopic dermatitis” in a test subject, thereby obviating the rejection with respect to Claim 1 and Claim 2 dependent thereof.

Rejection of Claims 1-3 and 31 Under 35 U.S.C. § 112 First Paragraph- New Matter

Claims 1-3 and 31 are rejected under 35 U.S.C. § 112, first paragraph for allegedly containing new matter. The Examiner states that “[t]he claims contain subject matter which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention”. (Office Action at page 4, paragraph 3, (6.)). Specifically, the Examiner states that “[t]he amendment amending the claim fails to site (sic) any support in the specification for the amended subject matter of the amended claim”. (Office Action at page 4, paragraph 4). In particular, the Examiner states that “[m]easurement of the expression levels of TR3 and TINUR is not described in the specification” and, further, that “the specification discloses that an elevation in TR3 or TINUR is indicative of an improvement and a decrease in eosinophils, as in the case of

atopic dermatitis.” (Office Action at page 5, paragraph 2). In addition, the Examiner states that the phrase ‘a sample containing eosinophils’ “reads on a whole blood sample” and that “Applicants have not described the gene expression of TR3 or TINUR in any cell type other than eosinophils in patients with atopic dermatitis”. (Office Action at page 5, paragraph 3).

The Specification clearly describes the claimed subject matter such that one of skill in the art would believe that Applicants were in possession of the invention at the time the application was filed. Specifically, the Specification discloses the measurement of the expression level of both TR3 and TINUR together in eosinophil cells, the increase in the expression level of the genes being indicative of atopic dermatitis. Applicants direct the Examiner’s attention to literal support found in the Specification in which it is stated that:

“The present inventors discovered that the expression level of the TR3 and/or TINUR genes increases in eosinophils of atopic dermatitis patients. Therefore, using TR3 and/or TINUR gene expression level as an index, tests for allergic disease can be performed on test subjects.”

(Specification at page 11, lines 29-33, emphasis added).

The Specification also summarizes the expression data for TR3 and TINUR, the results of which form the basis for the claimed method stating “[t]he present invention revealed that expression of the TR3 and TINUR genes increases in the eosinophils of atopic dermatitis patients.” (See Specification at page 20, lines 27-28). Thus, the Specification both presents data demonstrating that expression levels of both TR3 and TINUR are elevated in the eosinophils of atopic dermatitis patients and describes how measurement of the expression levels of TR3 and TINUR can be used to test for atopic dermatitis.

Claims 3 and 31 have been cancelled, thereby making the rejection moot with respect to those claims. Claim 1 has been amended to recite the expression level of a gene or genes encoding the TR3, TINUR or TR3 and TINUR receptor protein in “eosinophil cells” to more clearly describe the method.

Rejection of Claims 1-3 and 31 Under 35 U.S.C. § 103(a)

Claims 1-3 and 31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kremer *et al.*, WO 00/77202 and Mages *et al.*, 1994 in view of the abstract of Wedi *et al.*, 1997.

The Examiner states that “Kremer et al., teach NOT polypeptides, polynucleotides, therapy and diagnostic assays for such” but that “Kremer et al., do not teach atopic dermatitis.” (Office Action at paragraph spanning pages 6 and 7). The Examiner also states that “Mages et al., teach NAK1/TR3 and NOT expression in PMBCs... that Nur77/NAK-1/TR3 play a significant role in activation-induced apoptosis in T-cells and that functional inactivation of Nur77/NAK-1/TR3 completely abrogates apoptosis”. (Office Action at page 7, paragraph 2, citations omitted). The Examiner further states that “Wedi et al., teach that delayed eosinophil apoptosis is a common feature of allergic diseases, including atopic dermatitis.” (Office Action at page 7, paragraph 3). The Examiner concludes that based on the above teachings “it would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine the gene expression levels of TR3 or TINUR in samples obtained from test subjects containing eosinophil cells...”. (Office Action at page 7, paragraph 4). Moreover, the Examiner concludes that a person of ordinary skill in the art “would have been motivated to combine these teachings because a person looking to diagnose atopic dermatitis would have been motivated to look for aberrant gene expression of genes involved with dysfunctional apoptosis in eosinophils. ... (and) would have reasonably expected success because Kremer et al., successfully taught diagnostic assays of NOT/TINUR in lymphocytes and Mages et al., had been successful in determining the role of Nur77/NAK-1/TR3 in activation-induced apoptosis in T-cells, while Wedi et al., had already successfully shown delayed apoptosis in eosinophils was a common feature of atopic dermatitis.” (Office Action at page 7, paragraph 5).

Kremer *et al.* teaches polypeptides and polynucleotides of a splice variant of NOT1, so-called NOT1a, and discloses that it may be possible to diagnose diseases by determining if a sample from a subject has abnormally decreased or increased levels of a NOT1a polypeptide or mRNA using methods well known in the art for quantifying polynucleotides or polypeptides. Mages *et al.* teaches that NOT is a steroid receptor immediate early gene that is rapidly and transiently induced after mitogenic stimulation of T cells and is closely related to murine NURR1, rat RNR-1 and human NAK1/TR3. In the Discussion section, Mages *et al.* discloses findings by other investigators demonstrating that the NOT-related protein nur77/NAK1/TR3 “plays a preeminent role in activation-induced apoptosis of T cell hybridomas” and that the “functional inactivation of nur77/NAK1/TR3 totally abrogates apoptosis in this model.” (Mages *et al.*, at

page 1588, col. 2, paragraph 4). The abstract of Wedi *et al.* teaches that peripheral blood eosinophil programmed cell death is delayed in inhalant allergy and atopic dermatitis.

It would not have been obvious to one of skill in the art to combine the aforementioned references to arrive at Applicants' invention, nor would one of skill in the art have been motivated to combine such disparate and unrelated disclosures. Kremer *et al.* does not teach NOT1 (i.e., TINUR); instead, Kremer *et al.* teaches NOT1a, a splice variant of NOT1. As there are no data or teachings as to NOT1a characteristics nor any suggestions or showings that NOT1a shares any activities with NOT1, one of skill in the art would not be motivated to combine the teachings of Kremer *et al.* with *any* reference to arrive at Applicants' invention of measuring TINUR (NOT1) expression in eosinophil cells to test for atopic dermatitis, especially since, as acknowledged by the Examiner, "Kremer et al., do not teach atopic dermatitis." (Office Action at page 7, paragraph 1). Demonstration in Kremer *et al.* that NOT1a mRNA is expressed in lymphocytes (in addition to numerous other human tissues), does not teach one of skill in the art that NOT1a or NOT1 is expressed in eosinophil cells, which are a different cell type than lymphocytes, nor does it teach that NOT1a or NOT1 expression is changed (i.e., elevated) in a disease condition (i.e., atopic dermatitis). In fact, there are no teachings regarding any mutations in or aberrant expression of NOT1a, let alone NOT1, in association with *any* diseases and there are no teachings directing one of skill in the art how to obtain or produce such information. This information would be critical to practice a method of diagnosing a disease using the aberrant expression of NOT1a polynucleotides and/or polypeptides, even as vaguely as that described in Kremer *et al.* In other words, the generic disclosure of Kremer *et al.* regarding a NOT1-related gene, NOT1a, having unknown characteristics, does not begin to enable one of skill in the art to practice the claimed invention and, as such, can not make obvious Applicants' claimed method in view of the teachings of any reference, including those of Mages *et al.* or Wedi *et al.*

In addition, the disclosure of Mages *et al.* does not suggest Applicants' invention as Mages *et al.* does not teach or suggest NOT expression in *eosinophil cells*. Mages *et al.* teaches that NOT is expressed in T cells. T cells are not the same as eosinophil cells and thus, one of skill in the art would not believe that the induction of the expression of NOT in T cells upon mitogen stimulation would occur in eosinophil cells under the same conditions (i.e., mitogen stimulation), let alone under the conditions of atopic dermatitis, which are the conditions under which Applicants' claimed method is practiced. In fact, the Examiner makes this very point, stating that "there are numerous cell types with a whole blood sample, including monocytes, macrophages,

neutrophils, basophils, Tcells, Bcells, eosinophils, NK cells, and various dendritic cell precursors. ... Applicants have not described whether the TR3 or TINUR genes are expressed in a cell type other than eosinophils. ... measurement of cDNA...from a sample containing a mixed cell population would not provide an accurate or precise measurement of eosinophil gene expression...". (Office Action at page 5, paragraph 3).

Similarly, mention in Mages *et al.* of the involvement of nur77/NAK1/TR3 in activation-induced apoptosis of T cell hybridomas does not suggest to one of skill in the art Applicants' invention, which is a method of testing for atopic dermatitis by determining if the expression level of TR3 and/or TINUR encoding genes are elevated in the eosinophils of a test subject, simply because it was known in the art that eosinophil programmed cell death is delayed in atopic dermatitis, as disclosed in the abstract of Wedi *et al.* The Examiner states that "[a] person of ordinary skill in the art would have been motivated to combine these teachings because a person looking to diagnose atopic dermatitis would have been motivated to look for aberrant gene expression of genes involved with dysfunctional apoptosis in eosinophils." (Office Action at page 7, paragraph 4). However, allergic diseases are multi-factorial diseases in which multiple biological phenomena are controlled by multiple genes. In view of this, the Examiner fails to provide a clear line of reasoning explaining why the skilled artisan, based on the abstract of Wedi *et al.*, would have focused on dysfunctional apoptosis in eosinophil cells to devise a test for atopic dermatitis or how the skilled artisan would have logically arrived at Applicants' invention based on Kremer *et al.* and Mages *et al.* in view of the limited disclosure of Wedi *et al.*

Furthermore, the above disclosure of Mages *et al.* in no way suggests Applicants' claimed invention because Mages *et al.* discloses nur77/NAK1/TR3 induction and involvement in the apoptosis of T cell hybridomas. T cell hybridomas, which are clonal cell lines that are fusions of T cells and tumor cells (thymoma cells), are not the same as eosinophil cells and, further, do not actually exist *in vivo*; they are an engineered research tool. Moreover, there is no link between activation-induced T cell hybridoma apoptosis and eosinophil cell survival and/or apoptosis in atopic dermatitis. Study of the journal articles in which the work to which Mages *et al.* refers was done, makes clear that the model system of T cell hybridoma apoptosis used therein is unrelated to the apoptosis of eosinophil cells in allergic disease. Thus, both Woronicz *et al.* and Liu *et al.* (see enclosed Woronicz *et al.*, *Nature* 367:277-281, 1994 and Liu *et al.*, *Nature* 367:281-284, 1994) teach that Nur77 mRNA and protein expression is increased upon T-cell receptor engagement-induced apoptosis of T-cell hybridomas and immature thymocytes (via anti-TCR and/or anti-CD3 antibodies) and that nur77 expression is required for this T-cell receptor-mediated apoptosis (see

Woronicz *et al.* at page 277, Abstract and Liu *et al.*, at page 281, Abstract). It is concluded in Woronicz *et al.* that “[a]s apoptosis occurs during the negative selection of T cells, Nur77 may play a key role during T-cell development” (see at page 280, col. 1, paragraph 1). Liu *et al.* also teaches that their model system is believed to mimic the negative selection of T cells (see at page 281, col. 1, paragraph 1). Thus, both references teach that the apoptosis observed is believed to be a model of the apoptosis that occurs in T cells in a process of negative selection (i.e., the elimination of T cells that recognize self antigen in complex with major histocompatibility complex (MHC)). In contrast, eosinophils do not undergo negative selection; thus, the results of the above studies would not suggest to one of skill in the art that genes required in an apoptotic pathway in different cells (i.e., T cells) and in a process non-existent in eosinophil cells (i.e., negative selection), would be involved in the apoptosis (or lack thereof) of eosinophil cells in atopic dermatitis. Accordingly, one of ordinary skill in the art would not be motivated to extrapolate gene expression results (i.e., Nur77) from the aforementioned *in vitro* model system of T-cell apoptosis in negative selection to the *in vivo* behavior of the same gene in completely different cells (i.e., eosinophil cells), under completely different conditions (i.e., allergic disease and/or atopic dermatitis) to arrive at Applicants’ invention, an extrapolation that would be required in order to combine Mages *et al.* with Wedi *et al.*

Even if improperly combined, the disclosures of Kremer *et al.*, Mages *et al.* and Wedi *et al.* would teach away from Applicants’ claimed invention of testing for atopic dermatitis by measuring the expression level of TR3 and/or TINUR encoding genes and determining if the expression of the gene or genes is elevated compared to that in normal subjects. It is Applicants’ discovery and invention that the expression level of TR3 and/or TINUR is elevated in subjects with atopic dermatitis as compared to normal subjects. However, Mages *et al.* discloses that Woronicz *et al.* and Liu *et al.* teach that nur77/NAK1/TR3 expression is increased upon activation-induced T cell hybridoma apoptosis and that nur77 expression is unchanged in growing T cells (see Woronicz *et al.* at page 280, col. 1, paragraph 1), upon cytokine withdrawal (see Woronicz *et al.* at page 277, col. 2, paragraph 1) and is briefly elevated but not maintained upon mitogen stimulation (see Woronicz *et al.* at page 277, col. 2, paragraph 1). Wedi *et al.* teaches that there is delayed apoptosis of eosinophil cells in atopic dermatitis, that is, in those with atopic dermatitis, there is a lack of apoptosis of eosinophil cells under conditions where eosinophil apoptosis would be expected. Therefore, even if improperly combined for the reasons outlined above, one of skill in the art would conclude that in the absence of apoptosis (e.g., when apoptosis is delayed), nur77/NAK1/ TR3 expression would not be increased. Thus, based on the above

references, one of skill in the art would come to a conclusion opposite of that of Applicants' invention, that the expression of TR3 and/or TINUR are increased in the eosinophil cells of subjects with atopic dermatitis, even though these eosinophil cells may be characterized by an absence of apoptosis. In other words, based on the teachings of Woronicz *et al.* and Liu *et al.*, the skilled artisan would expect that the increased expression of TR3 and/or TINUR discovered by Applicants in the eosinophil cells of atopic dermatitis patients would induce apoptosis of those cells; however, Wedi *et al.* teaches that this is not the case and that, instead, apoptosis is delayed in the eosinophil cells of atopic dermatitis patients. Accordingly, one of skill in the art could not have combined the cited references to arrive at Applicants' claimed invention and, consequently, would have had no expectation of success in doing so. Moreover, as Mages *et al.* and Wedi *et al.* teach away from Applicants' results regarding TR3 and/or TINUR expression in eosinophils, the references can not suggest, teach or make obvious the claimed method of detecting atopic dermatitis in a subject by measuring TR3 and/or TINUR expression levels in a sample of eosinophil cells from a subject and determining if the expression level of the genes is elevated compared to their expression level in a normal subject.

Therefore, as Kremer *et al.* and Mages *et al.* in view of Wedi *et al.* do not teach or suggest Applicants' claimed invention and, as one of skill in the art would not be motivated to combine the references or have any expectation of success in doing so, Applicants' claimed method would not have been obvious to one of skill in the art. Accordingly, the invention fulfills the requirements of 35 U.S.C. § 103(a).

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance. Accordingly, it is requested that the rejections be reconsidered and withdrawn and that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

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Respectfully submitted,

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Dated: Aug. 11, 2006